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Anaplastic Transformation of Papillary Thyroid Carcinoma in Recurrent Disease in Regional Lymph Nodes: A Histologic and Immunohistochemical Study

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Background and Objectives: Although the prognosis of papillary thyroid carcinoma is favorable in most cases, recurrent disease in the regional lymph nodes is not uncommon, and some patients die of recurrent disease that ultimately becomes unresectable. We studied the proliferative activity of cancer cells in recurrent foci in lymph nodes to see whether repeated recurrences might result in anaplastic transformation of papillary thyroid carcinoma.
Methods: Fourteen patients with papillary thyroid carcinoma who underwent reoperation for recurrent disease in the regional lymph nodes more than once were the subjects of the study. The histologic findings and proliferative activity of carcinoma foci at each recurrence were studied histologically and immunohistochemically.
Results: There were higher incidences of histologic features of poorly differentiated thyroid carcinoma in the metastatic foci in the lymph nodes as it recurred repeatedly, and the labeling indexes of proliferating cell nuclear antigen (PCNA) and nuclear antigen Ki-67 (MIB-1) increased.
Conclusions: These observations suggest that papillary thyroid carcinoma may become more malignant, even undergo transformation to an anaplastic variety, as metastatic disease in the regional lymph nodes recurs repeatedly. *J. Surg. Oncol. 1999;70:45–48.*

KEY WORDS: proliferative activity; proliferating cell nuclear antigen (PCNA); nuclear antigen Ki-67 (MIB-1)

INTRODUCTION

Although the prognosis of papillary thyroid carcinoma is favorable in most cases, the incidence of lymph node metastasis of papillary thyroid carcinoma in Japan is up to 80% [1,2], and recurrent disease in the regional lymph nodes is not uncommon [3–5]. Some patients die of recurrent disease after repeated resection of tumors that ultimately become unresectable [6].

On the other hand, it is well known that papillary thyroid carcinoma may undergo transformation to a more malignant anaplastic variety [7–10], and this anaplastic transformation may be seen even in the metastatic disease in the regional lymph nodes [11]. The mechanism of this transformation, however, is not well understood.

We studied the proliferative activity of cancer cells within the recurrent foci in the regional lymph nodes to see whether repeated recurrences might result in anaplastic transformation of papillary thyroid carcinoma.

MATERIALS AND METHODS

The subjects of this study were 14 patients with papillary thyroid carcinoma who underwent reoperation more than once for recurrent disease in the regional

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TABLE I. Histologic Findings of Primary Cancer Foci in the Thyroid and Each of the Recurrences of Disease in the Lymph Nodes*

	Primary tumor	First recurrence	Second recurrence	Third recurrence	Fourth recurrence	Fifth recurrence	Sixth recurrence
Tall cell	4/14 (28.6)	5/14 (35.7)	5/14 (35.7)	5/9 (55.6)	3/3 (100)	1/1 (100)	1/1 (100)
Ground glass nucleus	5/14 (35.7)	5/14 (35.7)	5/14 (35.7)	4/9 (44.4)	1/3 (33.3)	0/1 (0)	0/1 (0)
Nuclear groove	11/14 (78.6)	12/14 (85.7)	11/14 (78.6)	9/9 (100)	3/3 (100)	1/1 (100)	1/1 (100)
Nuclear atypia	10/14 (71.4)	12/14 (85.7)	13/14 (92.9)	8/9 (88.9)	3/3 (100)	1/1 (100)	1/1 (100)
Inclusion body	6/14 (42.9)	3/14 (21.4)	5/14 (35.7)	2/9 (22.2)	1/3 (33.3)	0/1 (0)	0/1 (0)
Squamus metaplasia	1/14 (7.1)	4/14 (28.6)	2/14 (14.3)	3/9 (33.3)	1/3 (33.3)	0/1 (0)	0/1 (0)
Anaplastic feature	0/14 (0)	1/14 (7.1)	3/14 (21.4)	0/9 (0)	1/3 (33.3)	0/1 (0)	0/1 (0)
Psammoma body	6/14 (42.9)	2/14 (14.3)	3/14 (21.4)	1/9 (11.1)	0/3 (0)	0/1 (0)	0/1 (0)
Stratification of cells	6/14 (42.9)	12/14 (85.7)	12/14 (85.7)	7/9 (77.8)	3/3 (100)	1/1 (100)	1/1 (100)
Solid growth	8/14 (57.1)	7/14 (50.0)	11/14 (78.6)	8/9 (88.9)	3/3 (100)	1/1 (100)	1/1 (100)
Desmoplasia	9/14 (64.3)	12/14 (85.7)	11/14 (78.6)	7/9 (77.8)	2/3 (66.7)	0/1 (0)	0/1 (0)
Cystic change	2/14 (14.3)	1/14 (7.1)	2/14 (14.3)	2/9 (22.2)	0/3 (0)	0/1 (0)	0/1 (0)
Extranodal invasion		10/14 (71.4)	12/14 (85.7)	8/9 (88.9)	3/3 (100)	1/1 (100)	1/1 (100)

*Percentage in parentheses.

lymph nodes at Ito Hospital in the years 1993 through 1995. The characteristics of the primary cancer foci in the thyroid gland and of the recurrent disease in the lymph nodes each time were studied histologically. Expression of proliferating cell nuclear antigen (PCNA) and nuclear antigen Ki-67 (MIB-1) was studied immunohistochemically using the formalin-fixed, paraffin-embedded specimens to evaluate proliferative activity of cancer cells in both the primary focus in the thyroid gland and the recurrent disease in the lymph nodes.

The percentages of PCNA- or MIB-1–positive cells among 1,000 cancer cells were used as labeling indexes (%), and the correlation between the expression of these antigens and the number of recurrences was tested statistically by the Wilcoxon test.

Antibodies used for immunohistochemical study were monoclonal mouse antiproliferating cell nuclear antigen (PCNA) (PC10; DAKO, Glostrup, Denmark) and monoclonal mouse antinuclear antigen Ki-67 (MIB-1; Immunotech, Marseilles, France).

RESULTS

Histopathologic Findings

Higher incidences of the histologic features of poorly differentiated thyroid carcinoma, which is characterized by nuclear atypia, solid growth, stratification, and squamous metaplasia, were observed in the metastatic disease in the lymph nodes as it recurred repeatedly. Tall cells were also seen more frequently, and extranodal invasion became more prominent as the metastatic disease recurred over again. In two patients, anaplastic transformation was observed in the recurrent disease in the lymph nodes, at the first recurrence in one and the second recurrence in the other. In contrast, such cancer cell findings as ground glass appearance and intranuclear cytoplasmic inclusion did not increase in incidence, even after repeated recurrences (Table I).

Immunohistochemical Findings

The PCNA and MIB-1 labeling indexes increased as the metastatic disease in the lymph nodes recurred repeatedly (Table II). In one of the two patients with anaplastic transformation, the labeling PCNA and MIB-1 indexes in the last recurrence were 6.0% and 11.1%, and in the other they were 17.4% and 11.6% (Figs. 1 and 2). Statistically significant correlations were observed between PCNA- and MIB-1–labeling indexes and the number of recurrences (Figs. 1 and 2).

DISCUSSION

The prognosis of papillary thyroid carcinoma is favorable in most cases, and multivariate analyses demonstrate that lymph node metastasis and even surgical procedures are not prognostic factors [12–14]. However, recurrent

TABLE II. Thyroid Carcinoma: Changes in PCNA- and MIB-1–Labeling Indexes in the Primary Cancer Foci and Recurrent Disease in the Lymph Nodes

		PCNA			MIB-1		
	n	Range (%)	Mean (%)	*p*	Range (%)	Mean (%)	*p*
Primary tumor	14	1.3–4.7	2.63		0.1–2.8	0.61	
First recurrence	14	1.4–6.4	3.92	0.0092	0.3–8.2	1.50	0.0119
Second recurrence	14	3.2–17.4	6.00	0.0001	0.5–11.6	2.96	0.0005
Third recurrence	9	4.0–14.1	7.28	0.0005	0.3–9.4	2.77	0.0033
Fourth recurrence	3	5.4–9.3	7.50	0.0000	1.9–5.1	3.67	0.0001
Fifth recurrence	1	8.10			7.70		
Sixth recurrence	1	7.90			7.20		

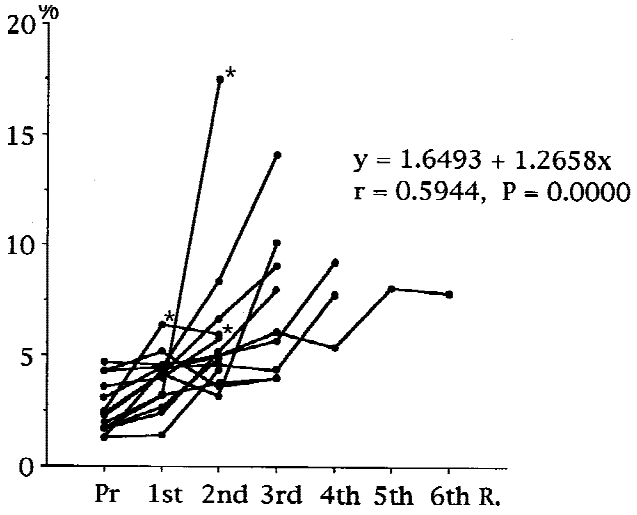

Fig 1. Changes in PCNA-labeling index in each case. Asterisks indicate patients with features of anaplastic transformation found in the recurrent disease in the lymph nodes. PCNA: proliferating cell nuclear antigen; Pr: primary tumor; R.: recurrence.

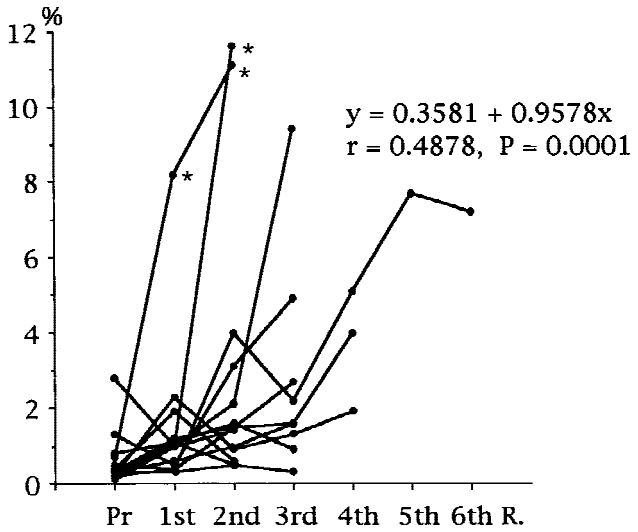

Fig. 2. Changes in MIB-1–labeling index in each case. Asterisks indicate patients described in the legend of Figure 1. MIB-1: nuclear antigen Ki-67.

disease in the regional lymph nodes is not uncommon [3–5], and some patients even die of recurrent disease in the regional lymph nodes after repeated recurrences that ultimately becomes unresectable [6].

Several factors may be involved in the recurrent disease in the regional lymph nodes becoming unresectable, namely, extension of metastatic disease to more distant lymph nodes, extranodal invasion to the carotid artery, trachea and esophagus, and rapid growth of metastatic disease after undergoing transformation to anaplastic carcinoma. In each circumstance this is thought to be the result of differentiated thyroid carcinoma cells acquiring more malignant characteristics. Frazell and Foote [6] warned early in 1958 that long-standing tumors can be expected to accelerate their invasive properties after years or decades of relative quiescence.

Anaplastic transformation of differentiated thyroid carcinoma to anaplastic carcinoma is well known [7–10], and even metastatic disease in regional lymph nodes can undergo anaplastic transformation [11]. Yamashita et al. [15] suggested that loss of peroxidase activity in cancer cells arising from thyroid follicular epithelium has some relationship to anaplastic transformation of these cells, but the true mechanism of differentiated thyroid carcinoma cells undergoing transformation to an anaplastic variety is still unclear.

Proliferating cell nuclear antigen is an intrinsic histologic marker in the G1/S phase of the cell cycle. Expression of PCNA often indicates the clinical behavior of thyroid neoplasms [16], and it can be used as a prognostic factor of differentiated thyroid carcinoma [17]. Similarly, nuclear antigen Ki-67 (MIB-1) is a human nuclear cell-proliferation-related antigen expressed by cells in active cell cycles. Immunohistochemically, the frequency of positive staining for MIB-1 is higher when thyroid carcinoma is more malignant [18,19].

The present study clearly showed increasing frequency of the histologic features of poorly differentiated carcinoma cells and higher PCNA and MIB-1 labeling indexes as the metastatic disease in the regional lymph nodes recurred repeatedly. These observations suggest that papillary thyroid carcinoma may become more ma-

lignant, even undergo transformation to an anaplastic variety, as the metastatic disease in the regional lymph nodes recurs over and over again.

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